DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

NDA 21-356, Viread

(tenofovir disoproxil fumarate) Tablets

Gilead Sciences

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Tara P. Turner, Pharm.D., Executive Secretary

Members
- John D. Hamilton, M.D.
- Princy N. Kumar, M.D.
- Roger J. Pomerantz, M.D.
- Sharilyn K. Stanley, M.D.
- Brian Wong, M.D.
- Ram Yogev, M.D.

Consultants (voting) Pending New AVAC Members
- Victor G. DeGruttola, Sc.D.
- Janet A. Englund, M.D.
- Jonathan M. Schapiro, M.D.
- Lauren V. Wood, M.D.

Consultants (voting)
- Henry G. Bone III, M.D.
- Barbara P. Lukert, M.D. (by telephone)

Patient Representative (non-voting)
- Robert J. Munk, Ph.D.

Industry Representative (non-voting)
- Eugene Sun, M.D.

Guests (non-voting)
- David Dorsky, M.D., Ph.D.
- Victoria A. Johnson, M.D.
- Pablo Tebas, M.D.

FDA
- Debra Birnkrant, M.D.
- James Farrelly, Ph.D.
- Mark Goldberger, M.D., M.P.H.
- Jeffrey Murray, M.D., M.P.H.
- Bruce Schneider, M.D.
- Kimberly Struble, Pharm.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GULICK: Good morning. I am Trip Gulick from Cornell. I would like to welcome you to this meeting of the Antiviral Advisory Committee.

I would like to start by having the members sitting around the table introduce themselves. Let's start with Dr. Sun. Please state your name and your affiliation.

DR. SUN: Eugene Sun, Abbott Laboratories.

DR. MUNK: Bob Munk, New Mexico AIDS InfoNet.

DR. TEBAS: Pablo Tebas, Washington University in St. Louis.

DR. JOHNSON: Vicki Johnson, University of Alabama at Birmingham.

DR. DORSKY: David Dorsky, University of Connecticut.

DR. POMERANTZ: Roger Pomerantz, Thomas Jefferson University, Philadelphia.

DR. BONE: Henry Bone, Michigan Bone and Mineral Clinic, Detroit.

DR. STANLEY: Sharilyn Stanley, Texas Department of Health.

DR. YOGEV: Ram Yogev, Children's Memorial Hospital, Chicago.

DR. HAMILTON: John Hamilton, Duke University and Durham VA Medical Center.

DR. KUMAR: Princy Kumar, Georgetown University, Washington, D.C.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. SCHAPIRO: Jonathan Schapiro, Stanford and Tel Aviv Universities.

DR. WONG: Brian Wong of the Westhaven V.A. and Yale University.

DR. DeGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

DR. ENGLUND: Janet Englund, Department of Pediatrics, University of Chicago.

DR. FARRELLY: Jim Farrelly, Pharmacology, FDA.

DR. SCHNEIDER: Bruce Schneider, Division of Metabolic and Endocrine Drug Products, FDA.

DR. STRUBLE: Kim Struble, FDA.

DR. MURRAY: Jeff Murray, FDA.

DR. BIRNKRANT: Debra Birnkrant, FDA.

DR. GOLDBERGER: Mark Goldberger, FDA.

DR. GULICK: Thank you. We also have Dr.

Lukert who was unable to attend but is going to be joining us by videoconference. I am not sure if she is actually hooked in or can hear us. We are assuming that she will be patched in at some point and when she is, we will stop and introduce her also.

I would like Tara Turner now to read the conflict of interest statement.

Conflict of Interest Statement

DR. TURNER: Thank you.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Dr. Roy Gulick,

Dr. John Hamilton, Dr. Princy Kumar, Dr. Henry Bone, Dr. Janet Englund, and Dr. Jonathan Schapiro.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Further, in accordance with 21 U.S.C. 355(n)(4), Dr. John Hamilton and Dr. Princy Kumar have been granted waivers that permit them to vote on matters related to today's discussions.

We would like to disclose for the record that Dr. Princy Kumar, Dr. Roger Pomerantz, Dr. Victor DeGruttola, and Dr. Jonathan Schapiro have interests which do not constitute financial interests within the meaning of 18 U.S.C. 208(a), but which could create the appearance of a conflict.

The Agency has determined, notwithstanding these interests, that the interest of the Government in their participation outweighs the concern that the integrity of the Agency's programs may be questioned. Therefore, Drs. Kumar, Pomerantz, DeGruttola, and Schapiro may participate fully in today's discussion and vote concerning Viread.

With respect to FDA's invited guest speakers, Drs. Victoria Johnson, Robert Munk, and Pablo Tebas have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Johnson would like to disclose that she has work on grants supported by GlaxoSmithKline and Bristol- Myers Squibb and is a medical consultant for GlaxoSmithKline and Bristol-Myers Squibb regarding HIV drug resistance. She has also received honoraria from Roche, Bristol-Myers Squibb, GlaxoSmithKline speakers bureaus.

Dr. Munk would like to disclose that he receives speaker fees from GlaxoSmithKline.

Dr. Tebas would like to disclose that he has been a local investigator in multi-center trials sponsored by GlaxoSmithKline and Bristol-Myers Squibb. He also believes that he once attended a GlaxoSmithKline advisory meeting.

In addition, we would like to note that Dr. Eugene Sun is participating in this meeting as an industry representative, acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. GULICK: Thanks very much.

I would like to call on Dr. Debra Birnkrant to give the introduction from the FDA.

Introduction/Opening Remarks

Debra Birnkrant, M.D.

DR. BIRNKRANT: Good morning. I would really like to welcome everyone to today's advisory committee meeting on tenofovir DF, and I really mean that from my heart, because I know it was very difficult for a lot of you to travel to get here and we really appreciate all of your efforts.

I would also like to mention that in

addition to our expert panel members, we have invited guests who are experts in the areas of HIV resistance and in bone metabolism, but before we get to today's scientific discussion, I would like to acknowledge three advisory committee members who are rotating off our committee.

They are Drs. Yogev, Pomerantz, and Hamilton, and we have certificates for your distinguished service.

Dr. Yogev is from Children's Memorial Hospital in Chicago, and he has served on our committee since 1997. We would like to thank him for all of his efforts and help during our deliberations. We have a certificate for him today. Why don't you come up and get your certificate, and you will be receiving a wooden plaque in the near future. Thank you very much.

[Applause.]

DR. BIRNKRANT: Dr. John Hamilton is from the Durham VA and from Duke University Medical Center. He has also served on our committee for the last four years, and we would like to thank him for his exemplary service.

[Applause.]

DR. BIRNKRANT: Dr. Pomerantz from Thomas

Jefferson University Hospital where I used to be a volunteer many years ago. We would like to thank him for his service, as well, and for helping us out during our last advisory committee meeting where he chaired the Valgan meeting.

[Applause.]

DR. BIRNKRANT: In addition, I would also like to acknowledge some of the new members who will be joining our committee as of November 1st. They are Dr. Victor DeGruttola from the Harvard School of Public Health, Dr. Janet Englund from the University of Chicago, Dr. Jonathan Schapiro from Stanford University, and Dr. Lauren Wood from NIH.

[Slide.]

Turning to today's discussion, as outlined in the background document received by the advisory committee members, we are convening this meeting today to discuss four key issues in the tenofovir DF NDA.

They are the treatment indication, the nonclinical and clinical assessment of the effects of tenofovir DF on bone, the resistance data contained in the NDA package, and the design of trials for traditional approval.

[Slide.]

The first issue I would like to elaborate on is the treatment indication. Gilead proposes the following treatment indication: Viread, in combination with other antiretroviral agents, is indicated for the treatment of HIV-infected adults.

This indication is based on analyses of plasma RNA and CD4 counts in two controlled trials in treatment- experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy. At present, there are no results from controlled trials evaluating the effect of tenofovir on clinical progression of HIV.

[Slide.]

This treatment indication is based on pivotal studies 902 and 907 which are contained in the NDA and were conducted in a treatment-experienced adult population. These trials were both designed as intensification strategies where either tenofovir or placebo were added to a stable antiretroviral regimen.

The treatment-experienced patients in these trials had a median duration of therapy of approximately 4 to 5 years. The mean baseline load was approximately 3.4 logs or 2,300 copies.

Mean baseline CD4 counts were 410 cells,

and participants in these trials had baseline mutations to all antiretroviral classes.

We will be requesting the advisory committee's input this morning and this afternoon regarding the labeled indication, that is, should it be broad as proposed by Gilead and as found in other labels of antiretroviral agents, or should it be limited to a treatment-experienced population.

[Slide.]

The next issue we would like to bring before you today has to do with the effects of tenofovir DF on bone, and the reason we are bringing this forward today is that bone mineral density reductions were seen, as well as osteomalacia, in multiple species in preclinical trials.

The mechanism is not fully defined, and you will hear more about the mechanism later today.

The clinical trial data were also limited for bone mineral density, so therefore, we will be seeking your advice regarding the implications of both the nonclinical and clinical data contained in the NDA, as well as recommendations for additional studies after you review the presentations regarding the extensive work that Gilead has done

with regard to preclinical testing and evaluation of the bone effects, as well as the clinical testing that is being conducted in Study 903. We will also ask you to comment on the monitoring plans and the clinical study.

[Slide.]

With regard to the virology data, the Viread NDA contains more virology data than any other NDA we have brought to this committee. There were many prospective and exploratory analyses conducted that evaluated the HIV RNA response by baseline phenotype and genotype, as well as number and type of thymidine analogue mutations at baseline. Therefore, we will be seeking your comments on the types of resistance analyses that were presented in the NDA, which ones should be used for future drug development and which ones should appear in the product labeling.

[Slide.]

Lastly, I would like to bring to your attention that we will be asking for your input with regard to the design of the traditional approval study, but I need to put that into the perspective of the accelerated approval regulations.

The Viread NDA was submitted in May of 2001 under the accelerated approval regulations, which allow for acceleration of approval of drugs for patients who have serious and life-threatening conditions, such as HIV, if they provide meaningful therapeutic benefit over existing therapies.

I would like to pause and commend Gilead at this point for studying Viread in the treatment-experienced population, a population with limited therapeutic options. This is definitely in keeping with the spirit of the accelerated approval regulations.

Under accelerated approval, a drug must have an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint other than survival or irreversible morbidity.

To that end, the Division of Antiviral Drug Products requires two adequate and well-controlled trials, such as 902 and 907, of 24 weeks duration to support accelerated approval, but in order for a product that is approved under the accelerated approval regulations to continue to be marketed, it must be subject to the need to confirm those findings found in the 24-week trials to

establish clinical benefit.

The way that we look at the durability of the benefit is that we require two studies to confirm the findings in the 24-week trials. That is, we require two studies of 48 weeks duration to support traditional approval.

[Slide.]

To date, Gilead has put forth Study 903, which is being conducted actually in naive subjects, and this trial is fully enrolled. It compares tenofovir DF to stavudine on a background of lamivudine and efavirenz.

I will mention here that the confirmatory traditional approval trials do not necessarily need to replicate the findings in the accelerated approval trials in the same populations. That is, for traditional approval, it is acceptable to have studies either in pediatrics or in a naive population if the accelerated approval was for a treatment-experienced population.

So, we will be seeking your advice regarding the design of the second traditional approval trial that Gilead has proposed, and this is in a pediatrics population.

[Slide.]

Lastly, I would just like to comment on today's agenda. Gilead will present first, and then the FDA will follow without a break for questions until after our break this morning, so that there is a continuity this morning.

Then, after the open public hearing, we will continue discussions and then pose the questions to the committee.

Thank you very much.

DR. GULICK: Thanks, Dr. Birnkrant.

I would like to turn now to the sponsor, Gilead Sciences, and their presentation.

Dr. Norbert Bischofberger will start.

Sponsor Presentation

Overview of Development Program

Norbert Bischofberger, Ph.D.

DR. BISCHOFBERGER: Good morning. My name is Norbert Bischofberger from Gilead Sciences. We are going to review the New Drug Application for tenofovir disoproxil fumarate.

[Slide.]

Joining us today are three consultants - Dr. Harry Genant from University of California at San Francisco, Dr. Jip Schooley, University of Colorado Health Sciences Center, and Dr. Steve

Teitelbaum, Washington University in St. Louis.

Due to an injury accident, unfortunately, Dr. Genant can't be physically with us today. He underwent surgery on Monday, but he is doing well and he is joining us by phone.

[Slide.]

In today's presentation, I will first review the preclinical data and the clinical development program. Dr. Jay Toole will then present to you efficacy, safety, and clinical virology data from our clinical studies. I will finish up our presentation with some concluding remarks.

[Slide.]

Despite the availability of a number of antiretrovirals today, there still exists a tremendous unmet medical need. When trying to construct a viable treatment regimen, both patient and their physicians face the challenge of drug resistance, pill burden, drug interactions, tolerability, and durability of treatment response.

Tenofovir disoproxil fumarate is a novel antiretroviral which addresses many of these challenges. Tenofovir disoproxil fumarate, or tenofovir DF, is an orally bioavailable prodrug of

tenofovir. Tenofovir contains a phosphomate.

It is an analogue of deoxyadenosinemonophosphate and as such, it is a nucleotide reverse transcriptase inhibitor. Tenofovir is dosed as one tablet, once daily, and it has a unique resistance profile showing durable activity against otherwise resistant viruses. This unique resistance profile is evident from in vitro cross-resistance studies.

[Slide.]

In vitro tenofovir retains activity against recombinant viruses expressing mutations at positions 67, 70, and 215, which are zidovudine resistant viruses. It also retains activity against recombinant viruses expressed in the L74V mutation, which are ddI resistant, against T69D, which are ddC resistant, and against Q151M complex, which are multinucleoside-resistant viruses.

Increased activity in vitro is observed against viruses expressing M184V or the 3TC resistance mutation.

From in vitro selection experiments, viruses expressing K65R emerged, and those viruses show a 3- to 4-fold reduced susceptibility to tenofovir.

[Slide.]

This unique resistance profile against recombinant viruses was confirmed when tenofovir was evaluated against HIV clinical isolates. Again, what was found is that 3TC resistant viruses with the M184V, ddI resistant viruses with L74V, and abacavir-resistant viruses expressing mutations at positions 74, 115, and 184 were slightly hypersusceptible to tenofovir with a mean 0.6- to 0.7-fold change from wild-type susceptibility.

Multinucleoside resistant viruses with Q151M or viruses expressing the tenofovir-associated resistance mutation K65R in general fell within the normal susceptibility range, which is less than 3-fold change from wild-type susceptibility.

High-level zidovudine resistant viruses, which express T215Y, in combination with other thymidine analogue mutations or TAMs, were either within the normal or the intermediate susceptibility range, which is less than 10-fold change from wild-type.

Finally, viruses expressed in the uncommon T69 insertion mutation were either within the normal intermediate or resistant susceptibility

range, and showed a mean 12-fold change from wild-type susceptibility.

[Slide.]

Tenofovir is administered as one tablet, once daily. Once-daily dosing is supported by the long intracellular half-life of tenofovir in human PBMCs, which is 10 hours in activated cells and 50 hours in resting cells. Once-daily dosing is also supported by the terminal pharmacokinetic serum half-life in humans, which is 17 hours.

Preclinical experiments showed that tenofovir is not a substrate or an inhibitor or an inducer of cytochrome p450, suggesting that it has a low potential to cause drug interactions with compounds undergoing hepatic metabolism.

This was indeed shown in Study 909, which found no clinically significant drug interactions of tenofovir DF with the NNRTI efavirenz or the PIs indinavir or lopinavir or ritonavir.

Tenofovir is renally cleared in a combination of filtration and tubular secretion. Study 909 also evaluated two nucleosides, 3TC and ddI, which undergo renal secretion, and the study found that co-administration of tenofovir DF with either 3TC or ddI did not affect clearance.

Finally, the oral bioavailability of tenofovir DF in humans ranges from 25 percent in the fasted state to 39 percent in the fed state.

[Slide.]

In vitro data from enzyme inhibition experiments or in tissue culture show that tenofovir does not affect mitochondrial DNA synthesis, mitochondrial DNA content, or lactic acid production, suggesting that there is a low potential for tenofovir to cause mitochondrial toxicity.

Toxicology studies in animals, which were designed to identify potential target organs in humans, suggested that GI, the kidney, and the bone as three such organs. The GI effect of tenofovir DF was a local, high-dose effect observed only in rats. These animals were administered a high dose of tenofovir, 1,000 mg/kg, in order to overcome the relatively low oral bioavailability in that species.

Nephrotoxicity was observed in dogs and monkeys, and it was characterized predominantly histologically by proximal renal tubular changes.

Finally, bone effects were observed in rats, dogs, and monkeys. The most significant

effects of tenofovir on bone were observed in juvenile monkeys which were administered a dose of tenofovir subcutaneously, which correlates to about 12- to 25-fold the human exposure.

These animals developed nephrotoxicity associated with bone abnormalities characterized histologically as osteomalacia. These bone abnormalities were reversible when either dosing was reduced or dosing was discontinued, and when these animals were started at the lower dose, correlating to about 4-fold the human exposure, and dosed up to three years, there was no radiographic evidence of any bone abnormalities.

Having identified the kidney and the bone as two potential target organs in humans, we instituted appropriate monitoring in all our clinical studies. As you will hear in the subsequent presentation by Dr. Jay Toole, there is currently no evidence of tenofovir DF-related, clinically significant nephrotoxicity or bone abnormalities in our clinical studies.

[Slide.]

Our safety database that was submitted with the NDA consisted of almost 1,000 HIV-infected patients who had received tenofovir DF 300 mg. At

the time of the NDA submission, which was May 1, 2001, we had data on approximately 150 patients who had received tenofovir DF 300 mg for at least 48 weeks.

At the time of the safety update, which was August 15, 2001, we had data on more than 600 patients who had received tenofovir DF 300 mg for at least 48 weeks.

I would now like to ask for Dr. Jay Toole to present to you the efficacy, safety, and clinical virology data from our clinical studies.

Clinical Trial Results

Jay Toole, M.D., Ph.D.

DR. TOOLE: Good morning. My name is Jay Toole. I will present the clinical trial results of tenofovir.

[Slide.]

We conducted three placebo-controlled studies. Study 901 evaluated tenofovir, short-term monotherapy, at four dose levels. Studies 902 and 907 were longer duration intensification studies in which tenofovir or placebo were added to existing background regimens.

We chose the intensification design because it allowed for the clearest demonstration

of the impact of a single agent in combination regimens.

Study 902 evaluated three dose levels, and Study 907, our Phase III study, evaluated the 300 mg dose for which we seek approval.

I will also present data for renal and bone parameters and from our clinical virology studies.

DR. GULICK: Dr. Toole, can I just stop you for a second.

[Interruption.]

[Recess,]

DR. GULICK: Welcome back. We are going to try to go on with the presentations this morning. After lunch, we are actually going to go to another room.

With apologies to our sponsor and thanks for their good humor throughout this, let's resume.

DR. TOOLE: If I could have the next slide, please.

[Slide.]

We will begin with Study 901, which was a randomized, double-blind, placebo-controlled, dose-escalation study of tenofovir monotherapy.

There were four dose levels studied

ranging from 75 to 600 mg/day.

To enroll, patients had to have HIV RNA greater than 10,000 copies/mL, and CD4 counts greater than 200.

There were 10 patients enrolled per dose level, 8 assigned to tenofovir and 2 to placebo.

A single dose was administered on day 1 for pharmacokinetic sampling. Then, after one week, 28 consecutive days of tenofovir administration. Both treatment-naive and experienced patients were enrolled in the study with the following baseline characteristics.

[Slide.]

Mean CD4 counts of 346 and 391, mean HIV RNA of 115,000 and 85,000; 36 percent of the patients in the placebo arm had prior treatment experience compared to 68 percent of patients in the tenofovir arm.

[Slide.]

Significant activity was observed, at the mean change from baseline to day 35, showed little change in the placebo group, a dose response with maximal activity observed in the 300 mg treatment group in which a 1.2 log reduction from baseline was observed.

Each of the treatment groups were statistically significantly different when compared with placebo, with p-values of less than 0.003. Dosing was discontinued on day 35.

[Slide.]

Following discontinuation, there was a slow return towards baseline. One week after dosing was discontinued, the 300 and 600 mg dose groups remained more than one-half log below baseline. This is consistent with a long intercellular half-life of the active moiety of tenofovir.

[Slide.]

To confirm the efficacy data in a larger number of patients, and to examine the long-term safety profile, we next conducted Study 902.

This was a randomized, double-blind, placebo-controlled study of tenofovir or placebo added to existing background regimens.

To enroll, patients had to have been on a stable background regimen for at least 8 weeks consisting of up to four approved antiretroviral agents.

Also, patients had to have HIV RNA greater than 400 and up to 100,000 copies/mL.

The primary efficacy endpoint was the time-weighted average change from baseline to week 24, also called DAVG24.

[Slide.]

Patients were randomized to one of three tenofovir dose groups or placebo in a 2:2:2:1 ratio. The double-blind phase was for 48 weeks, and after 24 weeks, patients randomized to placebo crossed over to 300 mg in a blinded fashion.After 48 weeks, all patients received 300 mg in an open label fashion for an indefinite period.

[Slide.]

186 patients were randomized and received tenofovir with the following baseline characteristics. Mean CD4 counts of 374 and a median HIV RNA of about 5,000/mL.

These patients were highly treatment experienced with a mean prior antiretroviral use of 4.6 years. Baseline genotyping was performed in this study, and identified resistance mutations associated with non-nucleosides in 32 percent of patients, protease inhibitors in 57 percent, and nucleosides in 94 percent of patients.

[Slide.]

Tenofovir was well tolerated. Disposition

of patients from zero to 24 weeks shows that 25 percent of patients discontinued study in the placebo arm compared to 9 to 16 percent of patients in the tenofovir arm.

Four percent of patients discontinued for an adverse event in the placebo arm compared to 4 to 10 percent of patients in the tenofovir groups.

There was one death in the study on the 75 mg dose group of tenofovir, and this was not attributed to tenofovir by the investigator.

[Slide.]

The disposition from zero to 48 weeks, which is the end of the double-blind phase, shows about 25 percent of the patients had discontinued the study, and importantly, the percentage of patients discontinued for an adverse event remained low, at about 10 percent, and was similar among the treatment groups.

[Slide.]

The primary efficacy endpoint was achieved as the mean DAVG24 showed little change in the placebo, and tenofovir at 300 mg resulted in a 0.58 log reduction from baseline.

About 30 percent of the patients in each of the treatment arms changed their background

regimen during the first 24 weeks of the study. To preclude the possible effect this would have on efficacy, on the efficacy outcome, we also conducted an analysis in the as-treated population for whom data were excluded following the period of change in the background regimen or study drug discontinuation.

The analysis of the as-treated population shows the 300 mg dose group at a 0.52 log reduction, and that remained statistically significant.

[Slide.]

The changes at week 24 appeared durable as the mean change from baseline in the 300 mg dose group at week 24 was approximately 0.6 logs below baseline, and that was durable out through week 48.

[Slide.]

There were no significant changes in CD4 cell counts at week 24, and at week 48, the changes in CD4 cell counts remained modest.

The safety profile of tenofovir was favorable.

[Slide.]

As the percent of patients with Grade 3 or 4 adverse events was 14 percent of patients in the

placebo group compared to 17 to 19 percent of patients in the tenofovir arms.

These are the adverse events which occurred at least 1 percent of patients and shows a generally similar profile between tenofovir and placebo. Through 48 weeks, there was no change in the profile and no adverse event appeared dose related.

[Slide.]

Grade 3 or higher laboratory abnormalities were more common in all the dose groups, occurring in 32 percent of patients in the placebo arm compared to 30 to 34 percent of patients in the tenofovir arms.

These are the laboratory abnormalities which occurred at least 1 percent of the patients and show a generally similar profile between tenofovir and placebo. Again, through 48 weeks, there was no change in the profile and no laboratory abnormality appeared dose related.

[Slide.]

Based on the safety and efficacy results in this study, we evaluated the 300 mg dose in Study 907, our Phase III study. This was a randomized, double-blind, placebo-controlled study

of tenofovir or placebo added to existing background regimens.

Similar to Study 902, to enroll, patients had to have been on a stable background regimen for at least 8 weeks consisting of up to 4 approved antiretroviral drugs.

Unlike Study 902, however, we attempted to minimize the amount of background switching or restricting the upper limit of baseline viral load to 10,000 copies/mL. This was successful in that only about 10 percent of patients in either treatment arm changed their background regimen during the first 24 weeks of this study compared to 30 percent of patients in Study 902.

The primary efficacy endpoint was DAVG24.

[Slide.]

Patients were randomized to tenofovir or placebo in a 2:1 ratio, and the double-blind phase was for 24 weeks, after which all patients received 300 mg in an open label fashion for an indefinite period.

[Slide.]

550 patients were randomized and received drug. At baseline, their characteristics were well matched with a mean age of about 40, about 15

percent of patients were female, and about 30 percent of patients were non-Caucasian.

Patients were also well matched with regard to whether their baseline, antiretroviral regimen contained either a protease inhibitor or a non-nucleoside.

[Slide.]

HIV characteristics were also well matched with median HIV RNA of about 2,300 copies and mean CD4 cell counts over 400. These patients were also highly treatment experienced with a mean prior antiretroviral use of approximately 5.5 years.

[Slide.]

A prospective virology substudy was performed in about half of the patients and identified baseline resistance mutations associated with non-nucleosides in about 50 percent of patients, protease inhibitors in about 60 percent, and nucleosides in 94 percent of patients.

[Slide.]

Tenofovir was well tolerated. Percentage of patients discontinuing through week 24 was 6 percent in both the placebo and the tenofovir arms. The percentage of patients who discontinued for an adverse event was also similar between tenofovir

and placebo with 3 percent of patients in each treatment arm discontinuing.

[Slide.]

The primary efficacy endpoint showed significant activity as the DAVG24 showed little change in the placebo group and a 0.61 log reduction in the tenofovir arm, and this was highly statistically significant.

[Slide.]

The mean change from baseline shows that the addition of tenofovir, one tablet, once daily, results in the rapid reduction from baseline in viral load to approximately 0.6 logs below baseline, and that is maintained out through week 24.

[Slide.]

Efficacy was also demonstrated in prospectively defined subgroup analyses. DAVG24 was analyzed according to patient's baseline HIV RNA of less than or greater than 5,000 copies/mL, CD4 counts of less than or greater than 200, male or female sex, or Caucasian or non-Caucasian ethnicity.

Tenofovir showed reductions of 0.4 to 0.7 logs and in each case, this difference was

statistically different compared to placebo.

[Slide.]

Secondary efficacy endpoints further confirmed the activity. The percentage of patients with HIV RNA less than 400 copies/mL was 13 percent In the placebo arm compared to 45 percent in the tenofovir arm. For HIV RNA less than 50 copies/mL, 1 percent in the placebo arm and 22 percent in the tenofovir arm. DAVG24 for CD4 cell counts shows an 11 cell decrease in the placebo and a 13 cell increase in the tenofovir arm.

[Slide.]

The safety profile of tenofovir was similar to placebo. Grade 3 or higher adverse events were reported in 13 percent of patients in the placebo arm compared to 14 percent of patients in the tenofovir arm.

These are the adverse events which were reported in at least 1 percent of patients in either treatment arm, and importantly, each of these events occurs in less than 1 percent of patients in the tenofovir arm.

[Slide.]

Grade 3 or higher laboratory abnormalities were reported in 37 percent of patients in the

placebo arm compared to 25 percent of patients in the tenofovir arm.

These are the laboratory abnormalities which occurred in greater than 1 percent of patients in either treatment arm and show a generally similar profile between tenofovir and placebo.

[Slide.]

Based on observations in animal studies, we were concerned about the potential for bone and kidney toxicity in tenofovir-treated patients. Because of that, we carefully monitored and conducted extensive analyses looking for these toxicities in our clinical studies.

For bone, we determined the bone fracture rate, and to assess the effects on the kidney we focused on changes in serum creatinine and phosphorus.

[Slide.]

I will present long-term data for these parameters from an integrated analysis of Studies 902 and 907.

In this analysis, there were 687 patients that received at least one dose of tenofovir 300 mg. 422 of these patients, as randomized, 191

patients following cross-over from placebo, and 74 patients following 48 weeks of either 75 or 150 mg in Study 902.

[Slide.]

480 of these patients had at least 48 weeks of tenofovir exposure and 156 patients had at least 72 weeks of tenofovir. The mean time on tenofovir was 58 weeks, and it ranged up to 143 weeks.

[Slide.]

The maximum toxicity grade for serum creatinine in Study 907 through 24 weeks shows a similar incidence of Grade 1 creatinine elevations between placebo and tenofovir, and there were no Grade 2 or higher creatinine abnormalities.

[Slide.]

Considering the longer term data, 5 percent of patients developed a Grade 1 creatinine abnormality while still no patient developed a Grade 2 or higher abnormality.

Our analysis indicates that these creatinine abnormalities are generally transient in nature.

[Slide.]

For the 32 patients with a Grade 1

creatinine elevation, 6 patients had the abnormality on a second consecutive visit. Of those 6 patients, only 1 patient had an additional 2 visits with the abnormality, and this patient discontinued the study secondary to pyelonephritis.

[Slide.]

Similar analyses were conducted for serum phosphorus. The maximum toxicity grade for hypophosphatemia in Study 907 in zero to 24 weeks shows 2 percent of patients in the placebo arm and 6 percent of patients in the tenofovir arm had Grade 2 hypophosphatemia. There were only isolated cases of Grade 3 or 4 abnormalities in either treatment arm. Six percent of patients in the tenofovir arm developed a Grade 2 abnormality through 24 weeks.

[Slide.]

Considering the longer term data with a mean of 58 weeks, that increased only slightly to 8 percent, while Grade 3 or 4 abnormalities remained uncommon. Our analysis indicates that the hypophosphatemia is also generally transient.

[Slide.]

For these 62 patients with Grade 2 or higher hypophosphatemia, 11 had two consecutive

visits with the phosphate abnormality, and only one patient had three consecutive visits. Two patients interrupted tenofovir for the hypophosphatemia, but no patient discontinued the study for hypophosphatemia. Overall, there is no indication of clinically significant nephrotoxicity associated with tenofovir.

[Slide.]

Regarding bone, the bone fracture rate is similar between tenofovir and placebo. For the 210 patients that received placebo, there was a total exposure of 99 patient years during which 3 fractures were reported, yielding a fracture rate of 3.0 per 100 patient years.

Considering the 687 patients that received tenofovir 300 mg, there was a total of 778 patient years of exposure during which 13 fractures were reported, yielding a fracture rate of 1.7 per 100 patient years.

[Slide.]

Radiographs from 12 of these 13 patients were available and reviewed by Dr. Harry Genant, Professor of Radiology at UCSF. He concluded these fractures were the result of high-impact trauma and not due to bone fragility. Also, for the cases for

which follow-up radiographs were available, normal bone healing was observed while tenofovir dosing was continued.

No vertebral compression fractures have been observed, and these are typically associated with osteoporosis. The tenofovir fracture rate is similar to placebo, and our analysis indicates that this rate has not increased with increasing tenofovir dosing duration.

[Slide.]

Overall, the safety profile of tenofovir 300 mg is similar to placebo through 24 weeks, and shows no significant change with extended dosing.

[Slide.]

Tenofovir 300 mg is a potent inhibitor of HIV replication and monotherapy resulted in a 1.2 log reduction from baseline. Tenofovir is active in highly treatment-experienced patients, and increased the percentage of patients that had HIV RNA less than either 400 or 50 copies/mL.

The activity is consistent across subgroups and appears durable through 48 weeks.

[Slide.]

As part of our efficacy evaluation, we also characterized the resistance profile of

tenofovir in our clinical virology studies. In this protocol-defined study, DAVG24 was analyzed according to whether a patient's HIV expressed at baseline the M184V mutations associated with lamivudine resistance, any thymidine analogue mutation, or TAM, or any primary non-nucleoside or protease inhibitor resistance mutation.

While little change was observed in the placebo, reductions of 0.5 to 0.7 logs were observed for tenofovir. In each case, this was statistically significantly different when compared to placebo.

[Slide.]

Of particular interest was the activity against TAMs. Thymidine analogue mutations are now widely recognized to play a crucial role in nucleoside treatment failure. There are six thymidine analogue mutations, and these are selected in patients receiving either zidovudine or d4T. In those patients, the selection of TAMs results in a reduced clinical response. TAMs also confer cross-resistance to ddI in the presence of the M184V mutation abacavir.

[Slide.]

In this exploratory analysis, the DAVG24

was analyzed according to baseline TAM expression. For patients with no TAMS, tenofovir resulted in a 0.8 log reduction from baseline, for 1 or 2 TAMs, a 0.66 log reduction from baseline, and for 3 or more TAMs, a 0.4 log reduction from baseline.

Upon further analysis, 3 or more TAMs, which included either the M41L or L210W TAM, showed a diminished response to tenofovir, but still remained statistically significant. For 3 or more TAMs, which did not include either the M41L or the L210W, a decrease of 0.67 logs was observed, similar to the overall study.

[Slide.]

In addition to genotypic analyses, we also conducted a phenotypic analysis. This is another exploratory analysis in which DAVG24 was analyzed according to the baseline HIV susceptibility to tenofovir relative to wild-type virus.

For reduced susceptibility of up to 4-fold, decreases of 0.5 to 0.7 logs were observed for tenofovir, whereas, a decreased response for a susceptibility of greater than 4-fold was observed.

[Slide.]

We also performed post-baseline genotyping to identify the development of resistance

mutations. Consistent with its activity, tenofovir suppressed the development of the mutations causing resistance to either protease inhibitors, non-nucleosides, or nucleosides.

While certain TAMs can cause a diminished response to tenofovir, tenofovir does not appear to select for TAM development. It does appear to select for the development of the K65R mutation as predicted from our in vitro studies, however, these arose in only 3 percent of patients.

[Slide.]

Overall, clinical virology substudies, we demonstrated that tenofovir is active against HIV, expressing common resistance mutations, including most TAMs. Also, there is a low incidence of tenofovir resistance mutation development.

[Slide.]

This is a highly favorable resistance profile and enhances tenofovir's other attributes, that it is safe and well tolerated, and it can provide durable antiviral activity.

[Slide.]

Based on the safety and efficacy data, tenofovir should be indicated in combination with other antiretroviral agents for the treatment of

HIV infection in adults.

Dr. Bischofberger, in his concluding remarks, will provide further rationale for this indication.

Phase IV Plans and Concluding Remarks

Norbert Bischofberger, Ph.D.

[Slide.]

DR. BISCHOFBERGER: Dr. Jay Toole presented to you efficacy, safety, and clinical virology data from our controlled studies 901, 902, and 907, and based on these data, we propose that tenofovir is indicated for the treatment of HIV infection in adults.

In order to further evaluate this indication, we need to consider the study design and the patient population studied.

[Slide.]

Both our pivotal studies, Study 902 and Study 907, were placebo-controlled intensification studies carried out in highly treatment-experienced patients.

The reason why we chose this design is that, first of all, this is the patient population with an unmet medical need. Secondly, the resistance profile of tenofovir allowed for the

addition of tenofovir alone as a single agent on the background therapy. Thirdly, such a placebo-controlled intensification design permits the clearest and most rigorous assessment of efficacy.

In these two studies, we were able to show that tenofovir has interviral activity in highly treatment-experienced patients, which, in general, is more difficult to achieve than in naive patients. However besides efficacy, tenofovir meets a number of other requirements which support its use in naive patients.

[Slide.]

One important consideration for the use of antiretrovirals in naive patients is adherence, its pill burden and the convenience of dosing. Tenofovir is administered as one tablet, once daily, and as such, meets that requirement.

Another important consideration is resistance development because not only can it lead to treatment failure, but it can also preclude future treatment options. Tenofovir has a lot potential for development of resistance mutations including TAMs.

Lastly, there is safety and tolerability.

Tenofovir DF has a safety profile similar to placebo over 24 weeks, and there is no evidence of any tenofovir DF related typical ART dose-limiting toxicities.

So, given the efficacy of tenofovir in treatment-experienced patients along with meeting some of these other requirements, tenofovir should be a treatment choice in naive patients.

We currently have three other studies either ongoing or planned that will give us efficacy and long-term safety data on tenofovir DF.

[Slide.]

The first such study is Study 910. This is a rollover study for our patients who completed Studies 901, 902, or 907. A total of 575 patients were enrolled in this study, and these patients will be followed up from December 2002 for safety, virology, and a subset of these patients for bone mineral density.

This will then give us over four years of experience for patients treated with tenofovir DF 300 mg.

[Slide.]

The second study is our Study 903. This is also our first confirmatory study. Study 903 is

a blinded, active-controlled study in antiretroviral and naive patients. The blinded portion of this study is of 96 weeks duration, and enrollment in this study was completed earlier this year, was 601 patients.

In this study, patients are randomized to one of two treatment arms consisting either of efavirenz, 3TC, d4T, or efavirenz, 3TC, tenofovir.

In this study, we are carrying out extensive bone evaluations in all 601 patients, consisting of bone mineral density analysis by DEXA scanning and following bone biomarkers for both the bone formation, which is osteocalcin, and bone-specific alkaline phosphatase, bone resorption, which is urinary N telepeptide in serum, C telepeptide.

In addition, we are also following vitamin D and parathyroid hormone.

This Study 903 constitutes our first confirmatory study. Our second confirmatory study is part of our pediatric development program.

[Slide.]

Our pediatric development program has recently been initiated following demonstration of safety of tenofovir DF in adults. A pediatric

formulation is currently in development, and will be available in the first quarter of next year.

We have two, Phase I/II studies, which will be initiated very soon. One is Study 926. This is a 48-week study looking at pharmacokinetics, safety, and efficacy in 24 pediatric patients. The protocol for this study has been signed off and the study will be carried out at the National Cancer Institute.

In addition, we have Study 927, which is a single and multiple dose PK study in 30 pediatric patients. This is a study that is going to be carried out at various centers in France.

As a Phase III study, a second confirmatory Phase III study, we have proposed to the Agency a 48-week placebo-controlled study of tenofovir DF added onto an optimized background regimen in pediatric patients who have failed previous therapies. This will then also constitute our second confirmatory study.

So, with these three studies, Studies 910, 903, and the proposed Phase III pediatric studies, we have three studies in place that will give us efficacy in an expanded population, and it will also give us long-term safety data particularly

with regards to the potential effects of tenofovir DF on bone.

In addition to these three studies, we have a number of other supportive studies planned including a study in renal and hepatic impairment and further drug interaction studies.

[Slide.]

So, with the data presented today, both preclinical and clinical, we demonstrated that tenofovir DF is an effective treatment of HIV infection.

Tenofovir DF is convenient, it is dosed once daily. It does not exhibit any clinically significant drug interactions. It has good tolerability with a safety profile similar to placebo over 24 weeks.

It has a favorable resistance profile both with regards to activity against resistant viruses and a low potential for development of resistance mutations including TAMs, and lastly, the treatment effect of tenofovir DF is durable through 48 weeks.

With that, I would like to thank you for your kind attention.

DR. GULICK: Thanks, Dr. Bischofberger and Dr. Toole for your presentations.

As we stated earlier, we would like to hold questions for the sponsor at this point and go ahead and proceed with the FDA presentation. Dr. Kim Struble is going to start.

FDA Presentation

Kimberly Struble, Pharm.D.

DR. STRUBLE: Thank you.

[Slide.]

My presentation will include an overview of the NDA submission followed by a summary of the efficacy and clinical virology results. Then, Dr. Jim Farrelly will give a summary of the nonclinical assessment of bone abnormalities. I will then conclude with a clinical assessment of the bone abnormalities, followed by a brief summary of the second study for traditional approval, and a summary of our regulatory issues.

[Slide.]

Gilead Sciences submitted a New Drug Application on May 1st of this year for the tenofovir DF 300 mg, given once daily, for the treatment of HIV infection.

[Slide.]

In this NDA submission, four clinical studies evaluating tenofovir tablets were

submitted, including two supportive and two principal studies.

The first supportive study, Study 901, was a 35-day, Phase II dose finding trial in treatment-naive and treatment-experienced patients.

Study 908 was a compassionate use safety study in patients with limited therapeutic options.

There are two principal studies, Studies 902 and 907. Both of these studies were randomized, double-blind, placebo-controlled for 24 weeks.

[Slide.]

The two principal studies, Studies 902 and 907, were both similar in design, the safety and efficacy of tenofovir compared to placebo when added to a stable antiretroviral regimen was assessed in treatment-experienced patients.

Both studies enrolled patients with similar baseline characteristics. Both studies were predominantly Caucasian men, approximately 41 years of age, and received about four or five years of prior antiretroviral therapy.

However, differences were noted in the two studies, and that was on the baseline HIV RNA. In Study 902, the baseline RNA was between 400 and

100,000 copies, whereas, in Study 907, the baseline RNA was restricted to between 400 and 10,000 copies.

Consequently, the mean baseline RNA was slightly higher in 902, and the mean baseline CD4 cell count was slightly higher in 907.

[Slide.]

The primary efficacy endpoint for these studies was the time-weighted change in log HIV RNA over 24 weeks or DAVG. We think that this analysis is useful for assessing any viral activity in which plasma levels below assay limit may not be frequently achieved.

Therefore, we concluded that DAVG is an acceptable endpoint for evaluating virologic responses in treatment-experienced patients, such as those enrolled in the two pivotal studies, Study 902 and 907.

Secondary endpoints include the proportion less than 400 and 50 copies.

[Slide.]

I will now show the HIV RNA results for the placebo and the tenofovir 300 mg dose group.

[Slide.]

This slide here shows the mean change from

baseline in HIV RNA over 24 weeks for Studies 902 and 907. As you can see, consistent results were seen in both studies. In both studies, statistically significant differences of approximately 0.5 to 0.6 log were seen for the primary endpoint favoring tenofovir over placebo.

In Study 902, the mean DAVG for the placebo group was an increase of 0.2 logs compared to a decrease of 0.58 logs for the tenofovir group.

In Study 907, the mean DAVG at week 24 for the placebo group was an increase of minus 0.02 log for the placebo group and a decrease of minus 0.61 log for the tenofovir group.

[Slide.]

This slide shows the proportion of patients less than 400 and less than 50. The less than 400 data is in yellow, and the less than 50 data is in orange.

In Study 902, numeric differences favoring tenofovir over placebo were seen at week 24. At week 24, the proportion of patients less than 400 was 19 percent in the tenofovir arm compared to 7 percent in the placebo arm.

The proportion of patients less than 50 was 11 percent in the tenofovir arm compared to

zero percent in the placebo arm.

In Study 907, statistically significant differences favoring tenofovir over placebo was seen for both analyses. At week 24, the proportion less than 400 was 40 percent for the tenofovir group compared to 11 percent for the placebo group.

For the less than 50 analysis, it was 20 percent for the tenofovir group compared to only 1 percent for the placebo group.

[Slide.]

I will now discuss the CD4 count results for the placebo and tenofovir 300 mg dose groups.

[Slide.]

This slide shows here the mean change from CD4 over 24 weeks in Study 902. This graph is a bit unusual in that the placebo group has a sharp increase at the last time point. This may, in fact, be due that there is only 22 patients available at week 24 and the data was quite variable.

The mean DAVG for this study was a decline of 11 cells for tenofovir group, and a decline of 4 cells for the placebo group. There were no differences between the two groups at any time point.

[Slide.]

This is the mean change for CD response for Study 907. The mean DAVG for the tenofovir group was an increase of 13 cells compared to a decrease of about 11 cells for the tenofovir group resulting in a net treatment difference of about 23 cells. Statistically significant results favoring tenofovir over placebo was seen at every time point.

[Slide.]

To further investigate the modest responses seen in these two studies, we looked at the CD4 cell count response by baseline CD4 from the pooled analysis of 902 and 907. We chose 200 cells because that was the protocol randomization scheme.

As you can see here, CD4 responses were similar for patients with less than 200 cells and greater than 200 cells. We felt that this finding was important for patients with lower baseline CD4 count cells for minimizing the risk of opportunistic infections over time.

[Slide.]

In summary, the mean viral load reductions we saw were similar for both studies, and

statistically significant differences of about 0.5 to 0.6 log favoring tenofovir over placebo were seen.

For the less than 400 and the less than 50 analysis, numerical differences favoring tenofovir over placebo was seen in 902, and statistically significant differences favoring tenofovir over placebo was seen in 907, however, there are modest increases in CD4 cell counts in Study 907, and no differences for CD4 counts between tenofovir and placebo were seen in Study 902 over 24 weeks.

[Slide.]

It is important to note that the study populations in Studies 902 and 907 may not have been optimal for observing large increases in CD4 cell counts, given the fact that only one new drug was added to a stable regimen.

The addition of one new agent did not produce a substantial increase in CD4 cell counts over time.

It is clear that further evaluations of CD4 responses in studies with different designs are needed.

[Slide.]

I will now go over the clinical virology

results.

[Slide.]

Prospective analyses were conducted by Gilead based on the HIV RNA response by prospectively defined baseline mutation subgroups in both Studies 902 and 907.

To further explore these issues, we conducted several exploratory analyses to further investigate RNA response according to the presence or absence of specific NRTI mutations. These analyses were done to determine if the specific mutations or mutational patterns affected response to tenofovir.

[Slide.]

However, it is important to note the limitations of these exploratory analyses in that the large number of potential comparisons does limit the ability to test for statistical significance.

Also, there was a limited number of patients for some primary NRTI and multi-drug resistant mutations to determine clinical significance.

Given these limitations, we are soliciting your feedback today on the types of exploratory

analyses conducted and recommendations for labeling.

[Slide.]

First, I will start out with the genotypic results.

[Slide.]

HIV RNA response by the presence or absence of thymidine analogue mutations was assessed. The six common thymidine analogue mutations, or TAMs, are defined as amino acid changes in positions 41, 67, 70, 210, 215, and 219.

[Slide.]

This slide here shows the mean HIV RNA response by baseline TAMs, specifically, the 67, 70, and 219. We see here that these mutations did not appear to affect tenofovir efficacy. In fact responses were similar regardless if these baseline mutations were present or absent.

[Slide.]

This slide here shows the HIV RNA response by the presence or absence of the 215, 210, and 41 mutation. It appears here that these mutations affect tenofovir efficacy and that responses were approximately 0.5 log less if these mutations were present at baseline.

We then conducted subsequent analyses to determine the impact of these mutations.

[Slide.]

In the previous slide, we showed that the 215 mutation appeared to affect tenofovir efficacy, but, in fact, it was felt that this mutation may not have directly impacted the overall results.

[Slide.]

Patients with the 215 mutation, along with the 41 or 210, had a mean DAVG of minus 0.25 logs. Compared to patients with the 215 without a 41 or 210, had a mean DAVG of minus 0.7 logs. Therefore, we concluded that it is the presence of the 41 or 210 mutation that affected response, and not necessarily the 215 mutation.

So overall, we concluded that it is the presence of the 41 and 210 mutation that affects overall tenofovir efficacy. Patients that do not have a 41 or 210 at baseline had a mean DAVG of minus 0.79 logs compared to patients with the 41 or 210 mutation, they had a mean DAVG of minus 0.26 logs at 24 weeks.

[Slide.]

It also appeared that the number and types of TAMs affected tenofovir efficacy. Patients that

had no TAMs at baseline had the largest declines in HIV RNA, and this subgroup had a mean DAVG of minus 0.8 logs.

Patients with one or two TAMs, or three or more TAMs, that did not include a 41 or 210, had approximately a mean DAVG of minus 0.65 log at week 24. Tenofovir actually appeared somewhat diminished in patients with three or more TAMs that included the 41 or 210. The mean DAVG for this subgroup was minus 0.21 logs.

[Slide.]

The 74 mutation also appeared to affect tenofovir efficacy. Eighteen patients expressed this mutation at baseline, and did not appear to respond to treatment. We also then evaluated this mutation to see if the presence or absence of other NRTI mutations actually affected response.

We found that the response rates were similar regardless if the 41 or 210 mutation was present along with the 74.

The 65 mutation was shown to reduce susceptibility to tenofovir in vitro. Six patients expressed this mutation at baseline, and did not appear to respond to tenofovir treatment over 24 weeks. However, more data is needed when patients

express this mutation to make any definitive conclusions at this time.

[Slide.]

Now, I will review the phenotypic results.

[Slide.]

Phenotypic analyses were done to determine if tenofovir baseline susceptibility affected response. Patients with tenofovir susceptibility within 4-fold or wild-type had a mean DAVG of minus 0.61 compared to patients with tenofovir greater than 4-fold or wild-type had a mean DAVG of minus 0.12, indicating that patients with reduced susceptibility to tenofovir at baseline had diminished activity.

[Slide.]

So, in summary, we concluded that the genotypic data suggest potential for some cross-resistance between tenofovir and specific NRTI mutations or patterns of mutations.

However, too few patients expressing some primary NRTI or multi-drug resistant mutations were available to determine clinical significance.

We agree with Gilead's analysis earlier presented in that no cross-resistance between tenofovir and lamivudine was seen.

[Slide.]

We also concluded that it was the presence of the 41 or 210 mutation that diminished tenofovir efficacy, whereas, mutations at positions 67, 70, 215, and 219 did not affect tenofovir efficacy.

The number and types of TAMs did affect tenofovir efficacy, and that these responses were reduced in patients with three or more TAMs, which included the 41 or 210.

The 65 and 74 mutation may also affect efficacy, and reduced susceptibility to tenofovir at baseline also diminishes tenofovir efficacy.

[Slide.]

Now, I will briefly describe the safety results. Treatment with tenofovir appeared to be well tolerated and similar to placebo. The most common adverse events associated with tenofovir use included asthenia, headache, diarrhea, nausea, and pharyngitis.

GI events, such as diarrhea, flatulence, nausea, and vomiting occurred greater in the tenofovir group compared to placebo.

In addition to these events, we also evaluated the nonclinical and clinical effects on bone abnormalities.

Now, Dr. Jim Farrelly will present the nonclinical assessment of bone abnormalities.

James G. Farrelly, Ph.D.

DR. FARRELLY: Good morning. My name is Jim Farrelly. I am the Pharmacology Supervisor in the Division of Antiviral Drug Products.

Today, I will present a compilation of bone toxicities discovered in the nonclinical toxicology safety studies carried out to support the use of tenofovir disoproxil fumarate or tenofovir DF in the clinic. Tenofovir DF is an esterified prodrug of tenofovir, which is a nucleotide analogue reverse transcriptase inhibitor and is rapidly converted to tenofovir in vivo.

As is the case for most new chemical entities submitted to an IND, the initial animal studies carried out to allow administration of tenofovir DF to human in a Phase I study were of a shorter duration than those carried out to support administration in a Phase II or a Phase II study.

Safety studies in a rodent and a non-rodent species are, as a general rule, expected by the Agency to support clinical dosing. In the submission of the original IND under which tenofovir DF was to be studied, a four-week safety

study in rats and a four-week safety study in dogs was submitted for review.

[Slide.]

Daily dosing for four weeks resulted in essentially no toxicity in rats dosed up to 500 mg/kg/day.

In dogs, doses up to 30 mg/kg/day showed minor toxicity in kidney, but no toxicity to bone. Thus, at the outset of a one-month clinical trial with tenofovir DF, bone toxicity in nonclinical studies was not seen yet, and therefore, was not a perceived concern.

[Slide.]

However, with longer term dosing, bone toxicity started to appear in the animal studies. In the rat, dosed up to a 1,000 mg/kg/day for 13 weeks, bone toxicity was seen, as well as adverse effects on the renal tubules. By 42 weeks, frank bone toxicity appeared at the two highest doses.

This toxicity presented as decreases in bone mineral content and density, cortical thickness of the femur, increases in deoxypyridinoline, a marker of bone resorption were found, as well as increase in osteocalcin, a marker of bone formation.

Plasma phosphorus increases, as well as increases in urinary calcium and phosphorus were found. Parathyroid hormone increases were also seen.

[Slide.]

Dogs, dosed daily up to 30 mg/kg/day for 13 weeks exhibited toxic effects in the kidney that was seen as tubular chiromegaly and chronic interstitial nephritis.

At 13 and 42 weeks, dogs dosed at 30 mg/kg/day exhibits bone toxicity presented as decreases in bone mineral content and density.

Changes in biochemical markers of bone metabolism, increased urinary N telepeptide, increased urinary calcium and phosphorus, increased bone specific alkaline phosphatase, and decreased 1,25-dihydroxy vitamin D3 were consistent with bone activation.

After a 13-week period in the absence of drug, there was some evidence of recovery.

[Slide.]

A 13-week gavage toxicology study in mice, carried out as a dose range-finding study for a two-year carcinogenicity evaluation was carried out.

No specific bone effects were seen in this study. Toxicity in the kidney and duodenum defined the maximum tolerated dose for the carcinogenicity study.

The carcinogenicity study has not been completed, but it will be interesting to examine it for the possible appearance of bone toxicities arising as the result of long-term chronic dosing, which would be in the fourth species.

[Slide.]

As the studies in rats and dogs were being carried out, the effects of tenofovir DF were being examined in monkeys. An early study dosed cynomolgus monkeys with tenofovir, not tenofovir DF, intravenously for 14 days at doses up to 25 mg/kg/day, which is approximately equivalent to a dose of tenofovir DF of 50 mg/kg/day based on molecular weight differences. No bone toxicities were seen in this study. There were, however, treatment-related effect in the kidneys of the monkeys.

[Slide.]

Shortly after the start of clinical trials of tenofovir DF, efficacy studies on the effect of tenofovir, again not tenofovir DF, in monkeys

infected with SIV were carried out and reported to the Agency.

Rhesus monkeys, some infected and some not infected with SIV, were dosed subcutaneously with tenofovir. Bone toxicities were seen in monkeys after greater than 10 months of daily dosing of 30 mg/kg/day.

[Slide.]

The toxicity was characterized as abnormal growth plates and trabecula of the femur and ribs. Also seen were bone deformities and displacements, rib fractures, reduced bone density and bone loss in the spine or pelvis.

The animals showed a moderate to marked reduction of serum phosphorus with elevate alkaline phosphatase levels. Non-hyperglycemic glucosuria and proteinuria were also seen. Serum calcium was unchanged, but unfortunately, urinary phosphorus and calcium were not measured.

Pregnant dams, dosed from the second trimester, gave birth to two offspring, but showed bone toxicity at 2 and 7 1/2 months of age. These animals, however, were dosed throughout the study at 30 mg/kg/day with tenofovir.

Other individual newborns, dosed for two

years with 10 mg/kg/day, showed no bone toxicity. The fact that bone toxicities were seen in the studies using monkeys prompted the Division to ask that special monitoring for bone toxicities in the 42-week studies in rats and dogs, as well as in the clinic, be carried out.

[Slide.]

These studies concluded that chronic treatment of rhesus monkeys at 30 mg/kg/day can result in a mineralization defect in developing and growing cortical bone consistent with a condition referred to as osteomalacia. The reversibility in the defect in mineralization was seen when the dose was reduced to 10 mg/kg/day or treatment was stopped.

[Slide.]

Finally, it should be stated that no bone defects were seen in a battery of four reproductive toxicology studies in rats and rabbits. In the studies, doses as high as 600 mg/kg/day in the rat and 300 mg/kg/day in the rabbit were administered.

The studies examined the effect of tenofovir DF on mating and fertility parameters in the rat, teratogenicity in the rat and rabbit, and peri- and post-natal development in the rat again.

[Slide.]

It is clear that tenofovir and tenofovir DF induce bone toxicities in three animal species. Toxicity is consistent with a diagnosis of osteomalacia, however, the mechanism whereby the toxicities arise is not known.

[Slide.]

The sponsor hypothesizes that the bone effects are secondary to a negative phosphate balance associated with drug-related impairment of intestinal phosphate absorption and/or renal reabsorption of phosphate, and not a direct toxic effect on bone.

The evidence based on animal toxicity studies, as well as in vivo and in vitro mechanistic studies presented by the sponsor up to this point, is consistent with the hypothesis, but at the present time, the mechanism must be considered to be unknown.

At this time, Dr. Struble will now continue with the Division's assessment of the submission.

Kimberly Struble, Pharm.D.

[Slide.]

DR. STRUBLE: After reviewing the exposure

data and bone abnormalities noted in the animal studies, it does give us some reassurance that there is a margin of safety for the proposed 300 mg dose in humans.

Bone mineral density reductions in rats and dogs were seen at 6 to 10 times higher than that of human exposures, and osteomalacia in monkeys was seen at 12 times higher than that of human exposures.

[Slide.]

We found no clinically significant changes in phosphate, calcium, PTH or bone mineral density observed over time in Studies 902 and 907, however, it is important to note that PTH and bone mineral density data was only available for a small subset of patients.

[Slide.]

In Study 902, the incidence of fractures was 5.5 percent. The proportion of patients with fractures in this study is higher than that seen in FDA meta-analysis of 13 trials in which patients who developed fractures was about 2 percent.

The observations seen in Study 902 may, in fact, be due to the small sample size, but further investigation of this potential safety signal was

warranted.

[Slide.]

This slide here shows the fracture rate in 6-month intervals. The fracture and patients is in white, and the rate and person years in 95 percent confidence intervals is in yellow.

We concluded that the fracture rate does not appear to increase over 6-month time intervals.

[Slide.]

So, after review of the entire nonclinical and clinical safety and pharmacokinetic data, we concluded that it is probably unlikely that tenofovir-related fractures would occur over 48 weeks.

This is assuming that the mechanism is mediated by renal phosphate wasting or decreases in intestinal absorption of phosphate.

We noted that no significant changes in renal parameters, in particular phosphate, were seen, and that incidence and severity of phosphate abnormalities did not worsen with increasing durations of tenofovir.

The rates of fractures did not appear to increase over 6-month time intervals. Review of the individual fracture data in Studies 902 and

907, we concluded that these fractures were probably a result of high trauma and accidental injury, and there did not appear to be an imbalance in fragility fractures.

[Slide.]

However, it is important to note that there are still insufficient numbers of patients receiving prolonged tenofovir treatment and a lack of a control arm past 24 weeks. It makes it difficult for us to conclude whether or not tenofovir would cause clinical fractures over time or if the risk would increase over time.

[Slide.]

Now, I will discuss the traditional approval plans.

[Slide.]

In general, we have required two studies assessing HIV RNA for a minimum of 48 weeks. Gilead has summarized their first study, Study 903, which compares tenofovir to d4T on a background of 3TC and efavirenz treatment in treatment-experienced patients for 96 weeks.

The second study they are proposing is a study in treatment-experienced children.

[Slide.]

This study is a two-part hybrid, and this study design was in part discussed at the January 2001 advisory committee on study designs and treatment-experienced patients. One hundred children will be enrolled in this study.

Children will have HIV RNA greater than 30,000 copies, CD4 percent less than 20 percent or less than 30 percent with an OI in the past 90 days. All children would have been experienced with at least one member of each drug class, and must be on a stable background regimen for at least 8 weeks prior to study entry.

At study entry, patients will be randomized to receive tenofovir or placebo over two weeks. At week 2, their stable background regimen will be changed to an optimized background regimen based on resistance testing conducted at baseline.

Patients would then continue on tenofovir or placebo for the remaining 46 weeks. The proposed endpoints for the study is the DAVG at week 2 and at week 48. The first part of the study assesses the contribution of tenofovir over placebo to a background regimen.

The second part of the study would assess the durability of tenofovir compared to placebo

when given with an optimized background regimen.

[Slide.]

Now I will discuss the summary of the regulatory issues, which we will discuss this afternoon.

[Slide.]

Gilead is seeking an indication for the treatment of HIV infection based on the results of Studies 902 and 907, however, the study populations in these studies were quite select given that they were both antiretroviral-experienced with a relatively low baseline viral load and high CD4 cell counts at entry.

[Slide.]

We are interested in the discussion this afternoon regarding the most appropriate indication for tenofovir - specifically, should it be given for the treatment of HIV infection, and that this indication would encompass the entire spectrum of HIV and disease including naive and treatment-experienced patients, or should tenofovir be recommended for the treatment of HIV infection in patients who have received prior antiretroviral therapy.

[Slide.]

The second issue relates to the bone abnormalities. The nonclinical data we saw reductions in bone mineral density in three different species, and the exact mechanism or mechanisms unknown, but it is probably due to renal phosphate wasting or decrease in intestinal absorption of phosphate.

[Slide.]

The clinical data, we saw no significant changes in phosphate, calcium, PTH, or bone mineral density over time, but again, PTH and bone mineral density was only available for a small subset of patients.

The rates of fracture did not appear to increase over 6-month intervals. It is clear that controlled safety data in more patients for longer durations are needed.

[Slide.]

We are interested in your assessment today of the nonclinical and clinical data with regard to bone effects. Gilead has also studied the bone abnormalities in several nonclinical studies. Also, Study 903 will provide comparative data for bone mineral density and bone biomarkers for approximately 600 patients over 96 weeks.

We would like to hear your recommendations today, if there are additional nonclinical or clinical studies that should be conducted to further evaluate tenofovir-associated bone abnormalities.

[Slide.]

With regard to clinical virology data, this NDA did contain more data than submitted for any other antiretroviral drug product. Both prospective and exploratory analyses were conducted, however, there were some limitations of the exploratory analyses conducted and presented today.

There are a limited number of patients for some primary NRTI and multi-drug resistant mutations to determine the true clinical significance.

Also, the large number of potential comparisons does limit the ability to conduct tests for statistical significance.

[Slide.]

We would like your comments today on the clinical resistance analyses conducted during the development of tenofovir, and would like to hear recommendations for the types of clinical virology

analysis that should be conducted for future antiretroviral drug development programs and suggestions for the type of resistance data and analysis that warrant display in package inserts.

[Slide.]

Regarding traditional approval and accelerated approval and Phase IV commitments, we would like your comments on the proposed second study for traditional approval in treatment-experienced patients.

Finally, we would like comments on other study designs or patient populations that should be studied as Phase IV commitments.

[Slide.]

Lastly, I would like to acknowledge and thank the entire tenofovir review team.

Thank you.

DR. GULICK: Thank you, Dr. Struble and Dr. Farrelly. Let's take a break now. Let's reconvene at five minutes of 11:00 and then we will proceed with the question period.

[Break.]

DR. GULICK: Welcome back, everyone. A couple of announcements. We changed our plans again and will have the meeting in this room all

day. We are not going to change rooms after lunch as we said before. We have given galoshes to Dr. Wong and DeGruttola.

One of the committee members joined us late. Dr. Wood, could you speak your name and where you are from.

DR. WOOD: I'm Dr. Lauren Wood and I am from the National Cancer Institute in Bethesda, Maryland.

DR. GULICK: Thanks. Dr. Lukert is out there in cyberspace. I am not sure we can hear her or if she can hear us.

Questions to Presenters

DR. GULICK: This is a period now for questions from the committee members and our guests. People can address questions either to the sponsor or to the agency. Dr. Pomerantz is taking the lead there, so we will let him start.

DR. POMERANTZ: It is my last committee meeting so I thought I would ask a couple of questions. Questions for the sponsor, I have a couple. First, you did say that there was a death in 902 and that it was not considered due to the drug, according to the investigator. Can you tell us what happened to that patient?

DR. TOOLE: That was a patient with a significant history of depression and, during the study, committed suicide with the ingestion of several toxic agents.

DR. POMERANTZ: Thank you. The second question is in 901, the monotherapy study. Was there any resistance data done prospectively or retrospectively on the primary or lack of resistance in those viruses?

DR. TOOLE: We did not see the development of any resistance mutations over the course of 28 days. Interestingly enough, we did do baseline genotyping. If you recall, we saw a somewhat lesser response in the 600 milligram dose group compared to the 300 milligram dose group and, retrospectively, we have identified it resulted from the presence of the M41L and study of other TAMs in two patients in the 600 milligram dose group.

DR. POMERANTZ: You don't know whether those viruses were primary-resistant in those patients or they developed it over time, I assume, primary resistance being transmission of a primary-resistant virus strain.

DR. TOOLE: We don't know that.

DR. POMERANTZ: The final thing, and I am sure this is going to let our endocrinological associates start off, but you had talked a little bit about the effects on the kidney and we saw some creatinine and such data. Were there any 24-hour urines or spot-urine lights done during those studies looking at phosphate, calcium, osmolality, the usual?

DR. TOOLE: We did studies looking at both calcium fractional secretion and phosphorous fractional secretion. In neither of those did we see significant changes when compared to placebo from baseline through week 24.

DR. POMERANTZ: Those were done in spots, or 24-hour urine--

DR. TOOLE: Those are spot collections.

DR. POMERANTZ: You have data for that?

DR. TOOLE: Yes.

Slide 257, please.

[Slide.]

The median change from baseline of phosphorous fractional secretion. These patients came in with phosphate fractional secretion of about 10 percent and, over the course of 24 weeks, there was no significant difference between placebo

and tenofovir.

256, please.

[Slide.]

In addition, now, with the extended data out beyond two years, there remained little change in the phosphorous fractional secretion.

DR. BONE: Excuse me. Can you show the previous slide?

DR. TOOLE: Slide 257, please.

[Slide.]

DR. BONE: That's it. Could I just chime in for a second on this. It does appear, however, that the fractional excretion of phosphorous is higher at every single time point in the treatment group than in the other group.

DR. TOOLE: Correct. But it was not significantly different between them.

DR. BONE: That would depend, actually. It wasn't significant at any one time point, but I suspect that, if a sign-ranked study had been used to look at the whole thing, the fact that there was a change in every case in the same direction would have led to a different conclusion.

DR. TOOLE: Correct.

DR. GULICK: Two reminders as we proceed

with the questions. One is, let's try to stick to questions on information right now, actually as Dr. Pomerantz showed us. So we will stick to the debating--we will leave those issues really until the afternoon. So stick to points of clarification or information.

DR. POMERANTZ: Just to finish that. You have no twenty-four hours urines on any of these patients, not only looking at calcium phosphate but osmolality, sodium, potassium.

DR. TOOLE: No; those are all spot analyses.

DR. GULICK: Dr. Kumar.

DR. KUMAR: I have a question regarding your safety data. Both you and the FDA showed that osteomalacia was seen in animals. But when you showed all the clinical data, both in 902 and 907, patients that were entered, the average age was 41 and there were only 15 persons--is there anything that you can tell us that shows that this safety data that you showed, there is no increase in fracture rate that we could take and say that older women, any data in the expanded access that you could show us that they did not have a higher fracture rate?

DR. TOOLE: The expanded access program has now enrolled 5000 patients in the U.S. and worldwide, 3000 patients in the U.S. That study began only in March of this year, and we have limited safety data on that study to date. We do have a compassionate access study, Study 908, which tenofovir was provided to patients with advanced HIV infection with CD4 counts less than 50.

At the time of filing, the mean duration on treatment was 44 weeks. In that study, the fraction rate was also similar to placebo. Again, there was no evidence of any clinically significant renal toxicity associated with tenofovir.

DR. KUMAR: But my question specifically was, in both 902 and 907, mainly it was mean and the age group was 41. My question is the older women are more susceptible to fracture, whether you had anything that you could see when you expanded that.

DR. TOOLE: No data are available yet on that. However, an important point to make is that postmenopausal women are more susceptible to fracture on the basis of osteoporosis. What we observed in our animal studies was osteomalacia.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: Could I look at the slide that you showed, Study 901, changes in viral load.

DR. TOOLE: 615, please.

[Slide.]

DR. SCHAPIRO: The week 35 comparison between the 300 and 600; the week 35 comparison between the 300 and 600 milligram dose, there were eight patients in each arm. Those included naive and experienced.

DR. TOOLE: Correct.

DR. SCHAPIRO: How many were actually experienced in that comparison?

DR. TOOLE: In the 300 milligram dose group, there were four treatment-naive and four treatment-experienced patients. The treatment-naive patients had a mean log change of 1.4 logs.

DR. SCHAPIRO: How many were experienced in the 600 milligram group?

DR. TOOLE: I don't recall.

DR. SCHAPIRO: So, actually, with the 300 and 600, we were comparing three to four treatment-experienced patients in each arm?

DR. TOOLE: Correct.

DR. SCHAPIRO: Could we see the CD4

results for those two groups?

DR. TOOLE: I didn't show the CD4 results for Study 901.

DR. SCHAPIRO: Do you have them? I would like to see them for those two doses.

DR. TOOLE: Slide No. 1, please.

[Slide.]

These are the mean changes in CD4 cell counts from baseline to Day 35. There was a lot of variability in this measurement. Of course, at 35 days, the placebo group is showing a 74 percent increase.

DR. SCHAPIRO: What would the explanation be for such a better response for 600 than for 300?

DR. TOOLE: I think the variability we are observing--this is probably based on the fact that there are very few patients enrolled. There were only eight patients per treatment group. The variability measurements reflected in these numbers. I don't think there is anything significant in the difference between the 300 and 600 milligram group.

DR. SCHAPIRO: But that is just based on the four to three experienced patients?

DR. TOOLE: No; these are the data for all

patients, all eight patients.

DR. SCHAPIRO: Were there any other data on 600 after this very small comparison?

DR. TOOLE: No.

DR. GULICK: Would you remind us of the median CD4 cell count on this study?

DR. TOOLE: Again, we don't have the medians. We did not pursue the 600 milligram dose after Study 901. That was based on--we also did an earlier study looking at intravenous and infused tenofovir. We administered doses at that 1 milligram per kilogram and 3 milligrams per kilogram. The 3 milligrams per kilogram dose corresponds to about five times the dose that received the 300 milligram oral dose and there were no significant log changes there after two weeks of dosing. They were in the 1.2, 1.4 log range. So they achieved maximum activity with the 300 milligram dose.

DR. SCHAPIRO: I bring this up because the drug-experienced patient in other drugs that we approve, we later found that different doses are appropriate ones. So it would be important to look into the drug-experienced patients to see--you showed the interaction--I think you mentioned that

a retonovir and lopinivir Kaletra was done, had an interaction?

DR. TOOLE: 126, please.

[Slide.]

So tenofovir caused a slight decrease in the Cmax, Cmin and AUC for lopinavir. So there was an approximately 15 percent decrease of lopinavir in both Cmax and AUC and a decrease of approximately 11 percent for Cmin. In discussions with the pharmacokineticist at Abbott and also with outside experts, this was deemed to be not clinically significant because the trough concentration still remains significantly above that required to inhibit the HIV replication in terms of both the IC50 and the IC90. I think the IC90 still remained more than 40-fold above that required.

DR. SCHAPIRO: Was that the drug-experienced patients or the drug-naive patients?

DR. TOOLE: This was done in naive type of patients.

DR. SCHAPIRO: So the levels you are measuring are the wild-type virus. Do you have an effect of Kaletra on tenofovir?

DR. TOOLE: There is an approximately 30 percent increase in this cohort of tenofovir AUC. We think that could be--that cohort was supposed to have taken tenofovir with food. And yet the AUC that we observed in this cohort was bit more consistent with tenofovir administered in the passive state. So now we are going to go back and reexamine that in more controlled study to see if there was interaction.

DR. SCHAPIRO: Since many patients received an higher active dose of retonovir, 400 milligrams, was there an interaction study--possibly if it is retonovir, we would see even a greater increase with three times the amount of retonovir.

Have any interactions been done with the 400 dose of retonovir? Has it been given to any of these patients?

DR. TOOLE: It has not been given.

DR. GULICK: Dr. Bone and then Dr. Stanley.

DR. BONE: Thank you. I have several questions in no particular order. In the clinical studies, you graded patients whose serum phosphorous fell to below 3.2 milligrams per

deciliter as Grade 1. In most laboratories, the lower limit of the reference range is about 2.5. I would be very interested in seeing the data for all patients who fell below 2.5 and all patients who fell by, say, 0.5 from their baseline as you did with one of the other measurements.

You probably don't have that at the moment, but I would like you to get that out. I am sure your statisticians can pull that out by this afternoon, unless you have it right now.

DR. TOOLE: No, but I will say that we used a central laboratory for all the clinical studies. The 2.2 was the lower limit of the normal for phosphorous in that central--

DR. BONE: Really. That is more than most laboratories' lower limit. So maybe you would look at the ones who fell by 0.5 or something like that because that is quite a low lower limit.

I think it would be interesting to see what the rate of decline of patients who had a declining serum phosphorous would be even if they were not frankly hypophosphatemic.

The second question has to do with the monkey study that was done at four times the predicted human dose. Do you have histology from

that study?

DR. TOOLE: No; we don't.

DR. BONE: You don't. So the only histology we have in monkeys demonstrates the osteomalacia at the higher dose. I guess that what you are telling me is that we don't have a no-effect dose for that histologic abnormality.

DR. TOOLE: The animals that were dosed at 10 milligrams per kilogram, and these are monkeys that began dosing at 2 mls, those monkeys had clear clinical observations in adult fractures. Bone biopsies were taken for those animals that had received the 10 milligrams per kilogram dose.

On dose reduction, on a 30 milligram per kilogram dose, animals that were begun as neonates at the 10 milligram per kilogram dose, and that is corresponding to about a fourfold increased level compared to the human dose, those animals are out more than two years now and there are no clinical findings which would indicate that these--at biopsy.

DR. BONE: But there has been no histologic examination.

DR. TOOLE: No histologic examination.

DR. BONE: So we don't have histology. We

don't have a no-effect dose demonstrated by histology; is that right?

DR. TOOLE: By histology; that is correct.

DR. BONE: In one of the FDA presentations, Dr. Farrelly's presentation, he mentioned that, in the dog study, the 42-week dog study, the 125 dihydroxy-vitamin-D levels were found to be reduced. Do you have similar information for any of your other studies?

DR. TOOLE: Vitamin D has not been assessed. Vitamin D is being assessed in the confirmatory study, Study 903.

DR. BONE: Surely you have samples.

DR. TOOLE: We were going to define a change in vitamin D levels in the course of Study 902, but we had an inadequate baseline sample in which to clear the further analysis.

DR. BONE: I think I will follow Dr. Gulick's recommendation and we will discuss that a little further later. Let's see. That is all for now. I will let somebody else take a turn. I will ask some more questions later.

DR. GULICK: Dr. Stanley and then Dr. Hamilton.

DR. STANLEY: Just a couple of things to

clarify. On the graph that you showed the decreased phosphate and increased creatinine kinase on only one visit, was that during the study continuing drug or was that after discontinuation of the drug?

DR. TOOLE: I'm sorry; which graph was that?

DR. STANLEY: No. 46 and I think 43, you said you had visits with grade 1 creatinine and--

DR. TOOLE: Those were all continuing on study. We monitored laboratory abnormalities while still on drug.

DR. STANLEY: So those were on drug.

DR. TOOLE: Yes.

DR. STANLEY: And then a question about the resistance data. You showed that, at 24 weeks, there was 3 percent occurrence of the K65R mutation. Have you looked at anything further out beyond 24 weeks and also, even at that time point, did you see any change in--any clinical susceptibility changes or in vitro changes?

DR. TOOLE: The response after the development of the K65R was typically variable. In Study 907, there were five patients who developed the K65R. In three of those patients, they had

little reduction in viral load from baseline. One patient developed the K65R but maintained a 0.7 log reduction. A fifth patient developed a K65R and showed a clear trend toward baseline. However, that patient also developed a primary non-nucleoside resistance mutation. That patient was also receiving nevirapine.

With regard to extended data, we have recent data which we have not yet shared with the FDA which will presented at ICAAC. In Study 902, there were 135 patients who entered the extension phase of dosing. We have now data on those 135 patients including 85 patients at week 96.

Through that time, we have developed--we have seen two more patients that developed the K65R. So the rate remains very low with extended dosing.

DR. STANLEY: Then my last question, for either the FDA or the sponsor. What are you defining--the approval has been requested for treatment in HIV-infected adults. What is the definition of age cutoff for adults that now we are using; thirteen or eighteen?

DR. STRUBLE: Eighteen.

DR. GULICK: Dr. Hamilton and then Dr.

Tebas.

DR. HAMILTON: I have a number of questions and a few points of clarification, particularly regarding the efficacy summary slide on Page 50 of the handout. Since the efficacy summary is often the only thing that people remember, I think it is important to know what each of those points represents.

So please tell me if I am mistaken here. It says, on the first point, tenofovir monotherapy for 28 days resulted in a 1.2 log copy ml change from baseline. Unless I am mistaken, that is based on six patients in Study 901 at the 300 milligram dose; is that correct?

DR. TOOLE: That's correct.

DR. HAMILTON: So, really, a more representative change would be those values reflected in 902 and 907 which are more like 0.5 and 0.6.

DR. TOOLE: That's correct except it is important to remember that 902 and 907 were intensification designs in which tenofovir was added as a single agent to a single baseline regimen whereas Study 901 was monotherapy for twenty consecutive days. So the 1.2 log reduction

was observed as monotherapy.

DR. HAMILTON: Secondly, in the subgroup analysis of those who fell by 450 copies per milliliter on Page 35 of the handout, those data are at 24 weeks; is that correct?

DR. TOOLE: That is the time-weighted average change from baseline to Week 24.

DR. HAMILTON: So that relates, then, to the last point, the final point, which says benefits are durable through 48 weeks. Have I just missed the 48-week data?

DR. TOOLE: That comes from Study 902. If I could have Slide 622, please.

[Slide.]

For the 300 milligram dose group, the plot of the mean change from baseline at Week 24, we saw a 0.6 log reduction. However, that was maintained out through Week 48 and that is where the durability to 48 weeks comes from.

DR. GULICK: May I remind committee members to speak into the mikes because people may be having trouble hearing.

Dr. Tebas and then Dr. Munk.

DR. TEBAS: I would like to ask you a couple of questions about your study that you

didn't present, and I have seen the results on Page 15 of the FDA summary. Can you tell us more about how those patients were selected? These were done at multiple sites or only one site? Was there a central reading for these or it was the reading at the site?

And, two, it seems as if you did between-arms comparison. You compared placebo with the tenofovir arm. Did you do a within-arms comparison? Did you compare the people that were randomized to tenofovir, the Week 24 to the baseline, because I don't think you have power to detect differences with placebo but maybe you have more power to detect differences within the same arm.

DR. TOOLE: The BMB substudy was done at multiple sites in both studies, 902 and 907. We concluded, and the FDA has also concluded, that there was no apparent dose response, so no dose response between the arms, between the different tenofovir dose groups. That was through 48 weeks of dosing.

After 48 weeks, all those patients in the substudy were receiving 300 milligrams.

DR. TEBAS: Was it a reading of--

DR. TOOLE: I'm sorry; that was a central location.

DR. TEBAS: Did you do a within-arms comparison?

DR. TOOLE: No; again, we didn't do that comparison but there was no apparent dose rsponse. In fact, the median change, after Week 24, was greatest in placebo. It was a -2 percent. Through Week 48, none of the treatment group showed a change greater than that.

DR. TEBAS: Say it again?

DR. TOOLE: The median change in bone-marrow density observed in Study in 902 at Week 24 was -2 percent. Through 48 weeks, all the doses showed a change which was less than that observed in placebo.

DR. TEBAS: Here in the placebo arm, the data on the table I see says the median change, 0.9 percent in the placebo arm increase and the tenofovir arm -0.7 percent decrease.

DR. TOOLE: Those are the data for studies 902 and 907.

DR. TEBAS: This is Page 15 in the FDA folder. In this folder, there is nothing on--

DR. GULICK: Which slide is that? Perhaps

we could have that slide?

DR. STRUBLE: What he is talking about is just this data in 902. We pooled the data from 902 and 907 so the exact percentages wouldn't be the same. So this is based on the pooled data whereas Dr. Toole is talking about what he saw in Study 902 alone.

DR. TEBAS: I see. Okay.

DR. GULICK: Dr. Munk?

DR. GULICK: Dr. Munk.

DR. MUNK: I am trying to get a little more understanding of the patient populations in 902 and 907. In 902, do you know how many patients had a viral load higher than 50,000?

DR. TOOLE: I don't know offhand, no. If your question is leading towards do we have activity in patients with higher viral load, the answer is yes, we have done that analysis.

DR. MUNK: Where is that?

DR. TOOLE: 388, please.

[Slide.]

We looked and saw the tenofovir had activity in patients who had the highest quartile baseline viral loads, and this was in Study 902.

There were 20 patients randomized to the

placebo group, and those 7 patients in the highest quartile with baseline viral loads had a mean baseline viral load of around 44,000.

For the 54 patients that were randomized to the 300 mg dose group, the highest quartile for those 14 patients, the mean baseline viral load was 76,000 copies per mL. The DAVG24 shows that there was little change in placebo and approximately a 0.5 log reduction in the tenofovir group. This is for the 300 mg.

DR. MUNK: And for the patients in those studies, you showed us the average length of time on antiviral treatment. Do you have information on the average number of previous agents that they had been exposed to?

DR. TOOLE: We just sorted that out by either greater than 4 or less than 4. I can find that data. I don't have those offhand. Most patients had at least 4 agents prior to therapy, but I don't know the exact percentages.

DR. MUNK: And did you collect any information on adherence?

DR. TOOLE: No, we did not.

DR. GULICK: Dr. Johnson.

DR. JOHNSON: I am going to extend on

those questions just to get a better understanding of the likelihood of finding a lot of resistance at baseline.

In your Study 902, you gave us, in the demographics, the median years prior ART experience. Could you comment on, for example, median number of prior regimens, which might get to how many sequences of agents patients had rolled through, and secondly, although the statement is made for both of those studies, 902 and 907, that baseline genotypic analysis revealed that 94 percent had one or more nucleoside-associated RT mutations, do you know how many were in the category of 2 or more, or 3 or 4 or more? I mean just 1 could be just a K70R that we might not care about, for example.

I am just trying to get at how much, what percentage of these patients at entry had lots of prior regimens and their history, and lots of baseline RT mutations.

DR. TOOLE: We didn't collect the data on exact number of prior regimens these patients have been exposed to, just on when they first started receiving antiretroviral treatment. With regard to the number of mutations at baseline, I will let Dr.